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<u>L2</u>	L1 same (prepar\$ or synthe\$ or biosynthe\$ or method of makin\$ or produc\$ or manufact\$)	270	<u>L2</u>
<u>L1</u>	acarbose	806	<u>L1</u>

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FILE 'BIOSIS, CAPLUS, MEDLINE, EMBASE, SCISEARCH, DRUGU, TOXCENTER,
PASCAL' ENTERED AT 14:21:02 ON 21 MAY 2003

L1	2 S ACARBOSE AND GLAUCESENS
L2	70 S ACARBOSE AND STREPTOMYCES
L3	39 DUP REM L2 (31 DUPLICATES REMOVED)

L3 ANSWER 31 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10

ACCESSION NUMBER: 1993:474003 BIOSIS

DOCUMENT NUMBER: PREV199396107603

TITLE: Alpha-glucosidase inhibitors of microbial origin.

AUTHOR(S): Selezneva, A. A.; Akulov, N. Yu.

CORPORATE SOURCE: All-Union Res. Technol. Inst. Antibiot. Enzymes, Moscow
Russia

SOURCE: Biologicheskije Nauki (Moscow), (1992) Vol. 0, No. 2, pp.
25-32.

ISSN: 0470-4606.

DOCUMENT TYPE: Article

LANGUAGE: Russian

SUMMARY LANGUAGE: Russian; English

AB The data on spreading of alpha-glucosidases with microbial origin are
given. Physicochemical characteristics of acorbose - a known inhibitor of
alpha-glucosidases - and new inhibitor isolated from **Streptomyces**
sp. are given in detail.

L3 ANSWER 30 OF 39 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:566290 CAPLUS

DOCUMENT NUMBER: 117:166290

TITLE: Rapid assay of glucoamylase using a
fluorescence-labeled glucoamylase inhibitor,
acarbose

AUTHOR(S): Hata, Yoji; Tanaka, Tatsuyuki; Suizu, Tetsuyoshi;
Kawato, Akitsugu; Abe, Yasushisa; Imayasu, Satoshi;
Ono, Kazuhisa; Oka, Satoru

CORPORATE SOURCE: Res. Inst. Gekkeikan, Gekkeikan Sake Co., Ltd., Kyoto,
612, Japan

SOURCE: Bioscience, Biotechnology, and Biochemistry (1992),
56(8), 1345-6

CODEN: BBBIEJ; ISSN: 0916-8451

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Usually, glucoamylase activity was assayed by measuring the rate of release of glucose from sol. starch. However, in routine anal. the ext. from rice-koji contains a large amt. of glucose and oligosaccharides, and these saccharides affect the assay of the glucoamylase activity. Therefore, the koji-ext. had to be dialyzed before the enzyme assay by the conventional methods. It has been reported however that the pseudooligosaccharides produced by **Streptomyces castaneglobisporus** inhibit fungal glucoamylases, and that affinity columns prepd. with the immobilized glucoamylase inhibitors, the pseudooligosaccharides or **acarbose**, effectively adsorbed glucoamylase from unpasteurized sake. These observations suggested that the substantially high affinity of the inhibitor for glucoamylase (**acarbose**, $K_i = 0.5 \mu\text{M}$; maltose, $K_m = 1.1 \text{ mM}$) might be applicable to the assay of the enzyme. In this study, a rapid assay method for glucoamylases was developed using a fluorescence-labeled glucoamylase inhibitor. **Acarbose** and 2-aminopyridine were chosen as a glucoamylase inhibitor and a fluorescent reagent, resp. 2-Aminopyridine was coupled to **acarbose**. From 1 mg of **acarbose**, 300 μg of purified pyridylaminated (PA-) inhibitor was eluted as a single peak on Shim-pack CLC-ODS (M) (4.6 mm \times 15 cm, Shimadzu), monitoring the glucoamylase-inhibitory activity and the fluorescent intensity. A protocol for glucoamylase assay using the fluorescence-labeled inhibitor is as follows. A glucoamylase soln. to be assayed was reacted with the PA-inhibitor, and then the glucoamylase-bound PA-inhibitor was removed from the reaction mixt. by an anion-exchange resin. Then, the glucoamylase activity in the sample was represented by the decrement in the fluorescent intensity (F_{dec}) that was given as the difference between the fluorescent intensity before (F_{int}) and after (F_{fin}) the elimination of the fluorescent affinity complex.

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L1 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:6349 BIOSIS
DOCUMENT NUMBER: PREV200200006349
TITLE: Isolation of the biosynthesis genes for
pseudo-oligosaccharides from streptomyces
glaucescens GLA.O, and their use.
AUTHOR(S): Decker, Heinrich (1)
CORPORATE SOURCE: (1) Bremtal Germany
ASSIGNEE: Aventis Pharma Deutschland GmbH, Frankfurt am
Main, Germany
PATENT INFORMATION: US 6306627 October 23, 2001
SOURCE: Official Gazette of the United States Patent and Trademark
Office Patents, (Oct. 23, 2001) Vol. 1251, No. 4, pp. No
Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB The invention relates to a recombinant DNA molecule which comprises genes
for biosynthesizing **acarbose** and homologous pseudo-
oligosaccharides; to oligonucleotide primers for the PCR amplification of
the molecule; to proteins which can be obtained by expressing the genes
located on a molecule; to vectors and host cells which comprise the
above-mentioned DNA molecule; to proteins which are encoded by the DNA
molecule; to proteins which are expressed by means of said vectors in said
host cells; to processes for preparing **acarbose** by introducing
the characterized genes into appropriate host organisms and/or eliminating
these genes from the host organisms; to processes for completing the gene
cluster of genes for biosynthesizing **acarbose**, to processes for
isolating analogous gene clusters in organisms other than Streptomyces
glaucescens GLA.O, to processes for mutating promoters of
endogenous **acarbose** biosynthesis genes for the purpose of
increasing the yield of **acarbose**, to the use of Streptomyces
glaucescens GLA.O for preparing **acarbose** and for
preparing mutants of Streptomyces **glaucescens** GLA.O which are
optimized with regard to the **acarbose** yield.

L1 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:8333 CAPLUS
DOCUMENT NUMBER: 128:72892
TITLE: Cloning of genes for biosynthesis of **acarbose**
and related pseudooligosaccharides from Streptomyces
glaucescens GLA.O and their uses
INVENTOR(S): Decker, Heinrich
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Ger. Offen., 36 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19622783	A1	19971211	DE 1996-19622783	19960607
WO 9747748	A1	19971218	WO 1997-EP2826	19970530
W:	AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			

AU 9731701	A1	19980107	AU 1997-31701	19970530
AU 728870	B2	20010118		
EP 915981	A1	19990519	EP 1997-927087	19970530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1223687	A	19990721	CN 1997-195885	19970530
BR 9709658	A	19990810	BR 1997-9658	19970530
JP 2001507923	T2	20010619	JP 1998-501137	19970530
US 6306627	B1	20011023	US 1998-194905	19980729
KR 2000016470	A	20000325	KR 1998-710054	19981205
US 2002192793	A1	20021219	US 2001-922683	20010807
PRIORITY APPLN. INFO.:			DE 1996-19622783 A	19960607
			WO 1997-EP2826 W	19970530
			US 1998-194905 A3	19980729

AB Genes for the enzymes involved in the biosynthesis of the .alpha.-amylase-inhibiting pseudooligosaccharide antibiotics such as **acarbose** are cloned from the producer organism *Streptomyces glaucescens* GLA.O. *S. glaucescens* is genetically well characterized in comparison to the *Actinoplanes acarbose* producers and so may be of greater use in the development of high-producer strains. The gene for dTDP glucose 4,6-dehydratase was cloned by PCR using primers derived from the sequence of previously characterized gene. This gene was used as a probe to obtain a 6.8 kb PstI fragment contg. six genes. The proteins encoded by three of these genes showed similarities to sugar-binding proteins that may be involved in the biosynthesis of **acarbose**.

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CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 13:18:41 ON
21 MAY 2003

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FILE 'EMBASE, SCISEARCH, BIOSIS, CAPLUS, MEDLINE, DRUGU, ADISCTI,
TOXCENTER, PASCAL' ENTERED AT 13:19:55 ON 21 MAY 2003

L2 1167 S L1 AND (PREPA? OR SYNTH? OR BIOSYNTH? OR PRODUCT?)
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L4 33 DUP REM L3 (38 DUPLICATES REMOVED)

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L4 ANSWER 14 OF 33 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:307342 SCISEARCH
THE GENUINE ARTICLE: 186VV
TITLE: The AcbC protein from Actinoplanes species is a C-7-cyclitol synthase related to 3-dehydroquinate synthases and is involved in the **biosynthesis** of the alpha-glucosidase inhibitor **acarbose**
AUTHOR: Stratmann A; Mahmud T; Lee S; Distler J; Floss H G; Piepersberg W (Reprint)
CORPORATE SOURCE: BERG UNIV GESAMTHSCH WUPPERTAL, GAUSS STR 20, D-42097 WUPPERTAL, GERMANY (Reprint); BERG UNIV GESAMTHSCH WUPPERTAL, D-42097 WUPPERTAL, GERMANY; UNIV WASHINGTON, DEPT CHEM, SEATTLE, WA 98195
COUNTRY OF AUTHOR: GERMANY; USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (16 APR 1999) Vol. 274, No. 16, pp. 10889-10896.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The putative **biosynthetic** gene cluster for the a-glucosidase inhibitor **acarbose** was identified in the producer Actinoplanes sp, 50/110 by cloning a DNA segment containing the conserved gene for dTDP-D-glucose 4,6-dehydratase, acbB. The two flanking genes were acbA (dTDP-D-glucose synthase) and acbC, encoding a protein with significant similarity to 3-dehydroquinate synthases (AroB proteins). The acbC gene was overexpressed heterologously in Streptomyces lividans 66, and the **product** was shown to be a C-7-cyclitol synthase using sedo-heptulose 7-phosphate, but not ido-heptulose 7-phosphate, as its substrate. The cyclization **product**, 2-epi-5-epi-valiolone ((2S,3S,4S,5R)-5-(hydroxymethyl)cyclohexanon-2,3,4,5-tetrol), is a precursor of the valienamine moiety of **acarbose**. A possible five-step reaction mechanism is proposed for the cyclization reaction catalyzed by AcbC based on the recent analysis of the three-dimensional structure of a eukaryotic 3-dehydroquinate synthase domain (Carpenter, E. P., Hawkins, A. R., Frost, J. W., and Brown, K. A. (1998) Nature 394, 299-302).

L4 ANSWER 2 OF 33 SCISEARCH COPYRIGHT 2003 THOMSON ISI
 ACCESSION NUMBER: 2002:532260 SCISEARCH
 THE GENUINE ARTICLE: 564KM
 TITLE: **Biosynthesis** of the C-7-cyclitol moiety of **acarbose** in Actinoplanes species SE50/110 - 7-O-phosphorylation of the initial cyclitol precursor leads to proposal of a new **biosynthetic** pathway
 AUTHOR: Zhang C S; Stratmann A; Block O; Bruckner R; Podeschwa M; Altenbach H J; Wehmeier U F; Piepersberg W (Reprint)
 CORPORATE SOURCE: Berg Univ Gesamthsch Wuppertal, Inst Chem Microbiol, Gauss Str 20, D-42097 Wuppertal, Germany (Reprint); Berg Univ Gesamthsch Wuppertal, Inst Chem Microbiol, D-42097 Wuppertal, Germany; Berg Univ Gesamthsch Wuppertal, Inst Organ Chem, D-42097 Wuppertal, Germany; Res Ctr Julich, Inst Biotechnol 1, D-52425 Julich, Germany
 COUNTRY OF AUTHOR: Germany
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (21 JUN 2002) Vol. 277, No. 25, pp. 22853-22862.
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
 ISSN: 0021-9258.
 DOCUMENT TYPE: Article; Journal
 LANGUAGE: English
 REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have previously demonstrated that the **biosynthesis** of the C-7-cyclitol, called valienol (or valienamine), of the α -glucosidase inhibitor **acarbose** starts from the cyclization of sedo-heptulose 7-phosphate to 2-epi-5-epivaliolone (Stratmann, A., Mahmud, T., Lee, S., Distler, J., Floss, H. G., and Piepersberg, W. (1999) J. Biol. Chem. 274, 10889-10896). **Synthesis** of the intermediate 2-epi-5-epivaliolone is catalyzed by the cyclase AcbC encoded in the **biosynthetic** (acb) gene cluster of Actinoplanes sp. SE50/110. The acbC gene lies in a possible transcription unit, acbKLMNOC, cluster encompassing putative **biosynthetic** genes for cyclitol conversion. All genes were heterologously expressed in strains of Streptomyces lividans 66 strains 1326, TK23, and TK64. The AcbK protein was identified as the **acarbose** 7-kinase, which had been described earlier (Drepper, A., and Pape, H. (1996) J. Antibiot. (Tokyo) 49, 664-668). The multistep conversion of 2-epi-5-epivaliolone to the final cyclitol moiety was studied by testing enzymatic mechanisms such as dehydration, reduction, epimerization, and phosphorylation. Thus, a phosphotransferase activity was identified modifying 2-epi-5-epivaliolone by ATP-dependent phosphorylation. This activity could be attributed to the AcbM protein by verifying this activity in S. lividans strain TK64/pCW4123M, expressing His-tagged AcbM. The His-tagged AcbM protein was purified and subsequently characterized as a 2-epi-5-epivaliolone 7-kinase, presumably catalyzing the first enzyme reaction in the **biosynthetic** route, leading to an activated form of the intermediate 1-epi-valienol. The AcbK protein could not catalyze the same reaction nor convert any of the other C-7-cyclitol monomers tested. The 2-epi-5-epivaliolone 7-phosphate was further converted by the AcbO protein to another isomeric and phosphorylated intermediate, which was likely to be the 2-epimer 5-epivaliolone 7-phosphate. The **products** of both enzyme reactions were characterized by mass spectrometric methods. The **product** of the AcbM-catalyzed reaction, 2-epi-5-epivaliolone 7-phosphate, was purified on a **preparative** scale and identified by NMR spectroscopy. A **biosynthetic** pathway for the pseudodisaccharidic acarviosyl moiety of **acarbose** is proposed on the basis of these data.

L4 ANSWER 3 OF 33 DRUGU COPYRIGHT 2003 THOMSON DERWENT
 ACCESSION NUMBER: 2002-34942 DRUGU P B

TITLE: **Preparation** and characterization of
 alpha-D-glucopyranosyl- alpha-acarviosinyl- D-glucopyranose,
 a novel inhibitor specific for maltose-producing amylase.
 AUTHOR: Kim M J; Lee H S; Cho J S; Kim T J; Moon T W; Oh S T; Kim J
 W; Oh B H; Park K H
 CORPORATE SOURCE: Univ.Seoul-Nat.Res.Cent.New-Bio-Mater.; Univ.Chungbuk-Nat.;
 Univ.Pohang-Sci.Technol.; Univ.Incheon
 LOCATION: Suwon, Cheongju, Pohang; Incheon, Korea
 SOURCE: Biochemistry (41, No. 29, 9099-108, 2002) 9 Fig. 4 Tab. 36
 Ref.
 CODEN: BICHAW ISSN: 0006-2960
 AVAIL. OF DOC.: Res. Cent. for New Bio-Materials in Agr. + Dept. of Food
 Science + Technol., School of Agr. Biotechnol., Seoul
 National University, Suwon 441-744, Korea. (K.H.P.). (e-mail:
 parkkh@plaza.snu.ac.kr).
 LANGUAGE: English
 DOCUMENT TYPE: Journal
 FIELD AVAIL.: AB; LA; CT
 FILE SEGMENT: Literature
 AB Alpha-D-glucopyranosyl- alpha-acarviosinyl- D-glucopyranose (GlcAcvGlc)
 and **acarbose** showed time-dependent inhibitions against
 maltogenase (MGase, Novo Nordisk), Thermus maltogenic amylase (ThMA) and
 cyclomaltodextrinase of alkalophilic Bac. sp. I-5 (CDase I-5, both
 purified from E. coli) in a mixture with p-nitrophenyl-alpha-D-
 maltoside (PNPG2) as substrate. Inhibition of ThMA and CDase I-5 by
acarbose or GlcAcvGlc followed mechanism B, while that of MGase
 followed mechanism A. **Acarbose** more efficiently inhibited
 maltase and sucrase from the rat intestine. Alpha-amylase from porcine
 pancreas was more sensitive to GlcAcvGlc than **acarbose**.
 GlcAcvGlc and **acarbose** did not inhibit sweet potato
 beta-amylase. GlcAcvGlc increased the dimeric form of ThMA. Therefore,
 development of **acarbose** derivatives as amylolytic enzyme
 inhibitors provides a new approach for the management of diabetes.